			ATTORNEY SOCKETNUMBER
RMP EV 11	TO-1390 -2000)	0(Modified) U.S. DEPARTMENTOF COMMERCEPATENTAND TRADEMARKOFFICE	PU3556USW
		ANSMITTAL LETTER TO THE UNITED STATES	U.S. APPLICATIONNO. (IF KNOWN, SEE 37 CFR
		DESIGNATED/ELECTED OFFICE (DO/EO/US)	
	(CONCERNING A FILING UNDER 35 U.S.C. 371	09/830037
TEF		IONAIAPPLICATIONNO INTERNATIONAIFILINGDATE 20 October 1999	PRIORITYDATECLAIMED 22 October 1998
TLU	EOF IN J TIC	NVENTION ASONE LOTION HAVING IMPROVED VASOCONSTRICTOR	ACTIVITY
Goi	rdon	T(S)FORDO/EO/US J. DOW; Keith Arthur JOHNSON; Frances Furr KELLY; Robert i RAJAGOPALAN	William LATHROP;
plic	cant h	nerewith submits to the United States Designated/Elected Office (DO/EO/US) th	e following items and other information:
1.	\boxtimes	This is a FIRST submission of items concerning a filing under 35 U.S.C. 371.	
2.		This is a SECOND or SUBSEQUENT submission of items concerning a filing	g under 35 U S.C. 371.
2. 3.	\boxtimes	This is an express request to begin national examination procedures (35 U S.C	
٥.	احب	(6), (9) and (24) indicated below.	
4.		The US has been elected by the expiration of 19 months from the priority date	(Article 31)
5.	\boxtimes	A copy of the International Application as filed (35 U S C. 371 (c) (2))	
		a. — is attached hereto (required only if not communicated by the International Communicated).	ional Bureau)
		b. 🛮 has been communicated by the International Bureau.	
		c. \square is not required, as the application was filed in the United States Rece	
5.		An English language translation of the International Application as filed (35 U	J.S.C. 371(c)(2)).
		a. is attached hereto.	'
		b. \square has been previously submitted under 35 U.S.C. 154(d)(4).	
7.	X	Amendments to the claims of the International Application under PCT Article	
		a. are attached hereto (required only if not communicated by the International Communicated)	ational Bureau)
		b \(\text{\text{\text{\text{\text{\text{b}}}}} have been communicated by the International Bureau.} \)	
		c. \square have not been made; however, the time limit for making such amend	ments has NOT expired
		d. Me have not been made and will not be made	
8.		An English language translation of the amendments to the claims under PCT.	Article 19 (35 U.S.C. 3/1(c)(3)).
9.	\boxtimes	An oath or declaration of the inventor(s) (35 U.S.C. 371 (c)(4)).	English and Bon out under DCT
0.		An English language translation of the annexes of the International Preliminar Article 35 (35 U.S.C 371 (c)(5))	y Examination Report under PC1
1.	\boxtimes	A copy of the International Preliminary Examination Report (PCT/IPEA/409)	
2.	\boxtimes	A copy of the International Search Report (PCT/ISA/210).	
I	tems	13 to 20 below concern document(s) or information included:	
13.	X	An Information Disclosure Statement under 37 CFR 1 97 and 1 98.	
١4.		An assignment document for recording A separate cover sheet in compliance	with 37 CFR 3.28 and 3 31 is included
15.	\boxtimes	A FIRST preliminary amendment	
16.		A SECOND or SUBSEQUENT preliminary amendment.	
17.		A substitute specification.	
18.		A change of power of attorney and/or address letter.	
19.		A computer-readable form of the sequence listing in accordance with PCT Ri	
20.		A second copy of the published international application under 35 U.S.C. 15	
21.		A second copy of the English language translation of the international applica-	ation under 35 U.S.C. 154(d)(4)
22.	\boxtimes	Certificate of Mailing by Express Mail	
23.	\boxtimes	Other items or information:	
		Copy of PCT Request (Form PCT/RO/101)	
ļ		Copy of PCT Publication cover Copy of Correction to PCT Request before 30th Month	

PCTUS1/REV03

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J.S. APPL	ICATION 9	00 (IF KNOWN, SEE 37 CFR 8 3 0 0 3 7	INTERNATIONALAP PCT/GB9	PLICAT	ION			ATTORNEY'SI	OOCKETNUMBER 6USW
24.	The follo	owing fees are submitted:.					CA	LCULATIONS	PTOUSEONLY
BASIC NA	ATIONAL	FEE (37 CFR 1.492 (a) (1) - (5)) :						
inte	ernational	national preliminary examinat search fee (37 CFR 1.445(a)(onal Search Report not prepar	2)) paid to USPTO			\$1000.00			
US	SPTO but I	preliminary examination fee nternational Search Report p	repared by the EPO or JPO			\$860.00			
but	t internatio	preliminary examination fee nal search fee (37 CFR 1 445 preliminary examination fee	S(a)(2)) paid to USPTO			\$710.00			
but	t all claims	did not satisfy provisions of preliminary examination fee	PCT Article 33(1)-(4).		•	\$690.00			
and	d all claim	s satisfied provisions of PCT	Article 33(1)-(4)		~ ~ ~	\$100.00			
			RIATE BASIC FEI					\$860.00	
nonths fro	om the ear	0 for furnishing the oath or dhest claimed priority date (3	7 CFR 1.492 (e)).	20)	□ 30		\$0.00	
CLAIM	AS	NUMBER FILED	NUMBER EXTR	RA .	x	\$18.00		\$72.00	
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	ent claims	Claims (check if applicable)					-	\$0.00	
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☐ Appl	licant clair iced by 1/2	ns small entity status. (See 3'						\$0.00	
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Processing months fr	g fee of \$1 rom the ear	30.00 for furnishing the Engliest claimed priority date (3	lish translation later than 7 CFR 1.492 (f)).	□ 20	0	□ 30 +		\$0.00	
			TOTAL NATI	ONAI	F	EE =		\$1,012.00	
Fee for re	ecording th	e enclosed assignment (37 C appropriate cover sheet (37 C	FR 1.21(h)). The assignme CFR 3.28, 3.31) (check if a	nt must l	be e).			\$0.00	
			TOTAL FEES			SED =		\$1,012.00	
							Am	ount to be: refunded	\$
								charged	\$
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b.	✓ Plea	se charge my Deposit Accour	nt No. 07-1392				12.00	to cover t	he above fees.
c.	The control of the second of t								
d.	The AMADAMAC I Compare on the form may become public Credit and								
NOTE: 1.137(a)	Where an or (b)) mi	appropriate time limit und ast be filed and granted to a	ler 37 CFR 1.494 or 1.495 estore the application to p	has not pending	bee stat	n met, a petit us.	tion 1	to revive (37 CF	R
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Page 2 of 2

April Zo 2001

DATE

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

Gordon J. DOW, et al

International Application No.:

PCT/GB99/03472

International Filing Date:

20 October 1999

Title: FLUTICASONE LOTION HAVING IMPROVED VASOCONSTRICTOR

ACTIVITY

Commissioner of Patents Washington, D.C. 20231

FIRST PRELIMINARY AMENDMENT

Dear Sir:

The above identified application is being transmitted herewith for entry in the US National Phase under Chapter II of the PCT for the purpose of adding the priority information. Please amend the application as follows:

In the Abstract:

Please substitute the attached Abstract, which has been placed on a separate sheet of paper according to US practice, as required under 37 CFR 1.72(b)

In the Specification:

On the first line of the specification, after the Title, please add:

--This application is filed pursuant to 35 U.S.C. §371 as a United States National Phase Application of International Application No. PCT/GB99/03472 filed 20 October 1999, which claims priority from GB9823036.0 filed 22 October 1998.--

REMARKS

Applicants have attached an abstract on a separate sheet of paper as required by US practice. Applicants haveamended the specification for purposes of adding the priority information. It is respectfully submitted that

the present application is in condition for allowance. An early consideration and notice of allowance are earnestly solicited.

Respectfully submitted;

James P. RIEK,

2. April 2001

Attorney of Record, Reg. No. 39,009

GlaxoSmithKline

Corporate Intellectual Property Department

Five Moore Drive, PO Box 13398

Research Triangle Park, NC 27709

Telephone: 919-483-1240/Fax: 919-483-7988

FLUTICASONE LOTION HAVING IMPROVED VASOCONSTRICTOR ACTIVITY

ABSTRACT

A fluticasone lotion having improved vasoconstrictor and anti-inflammatory activity and higher than expected potency. The fluticasone lotion contains 0.05 weight percent fluticasone propionate and an oil-in-water vehicle that includes excipients. The fluticasone lotion is unexpectedly efficacious while exhibiting an improved safety profile.

Via Facsimile

TO:
PCT Examination
PC1 Examination
International Bureau of WIPO
34 Chimin des Colombettes
1211 Geneva 20
Switzerland

Correction to PCT Request before 30th Month

Fax: 011 41 22 740 1435	
Applicant's File Reference	Applicant
PU3556WO	Glaxo Group Limited
International Application No.	International Filing Date:
PCT/GB99/03472	20 October 1999
30th Month Deadline: 22 April 2001	Title: Fluticasone Lotion Having Improved
-	Vasoconstrictor Activity

Correction:

Please make the following correction to PCT Request PCT/GB99/03472 filed on 20 October 1999.

-Please change address of inventors/applicants: <u>Keith Arthur JOHNSON</u>; <u>Frances Furr KELLY</u>; Robert William LATHROP and <u>Rukmini RAJAGOPALAN</u> to:

GlaxoSmithKline c/o Corporate Intellectual Property Department Five Moore Drive PO Box 13398 Research Triangle Park, NC 27709

Please acknowledge receipt of this request by return fax to (919) 483-7988 in the United States. If there should be questions, please call (919) 483-2252.

Thank you.

Sincerely,

Christopher P. Rogers Attorney for Applicant



TOPETEND OF APARTIC

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FLUTICASONE LOTION HAVING IMPROVED VASOCONSTRICTOR ACTIVITY

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FIELD OF THE INVENTION

The present invention is generally directed to a lotion comprising fluticasone.

BACKGROUND OF THE INVENTION

Fluticasone propionate is a steroid having anti-inflammatory, anti-pruitic, and vasoconstrictive properties. Fluticasone propionate cream (0.05%) is sold under the tradename CUTIVATE® cream. Each gram of CUTIVATE® cream (0.05%) contains 0.5 mg fluticasone propionate in a base of propylene glycol, mineral oil, cetostearyl alcohol, ceteth-20, isopropyl myristate, buffers and preservatives.

Mineral oil is a known occlusive agent. Occlusion in topical drug delivery is known to increase the vasoconstrictor potency of the topical steroid. By increasing the vasoconstrictor potency, the effectiveness of the steroid is increased. However, occlusive agents such as mineral oil can reduce the aesthetic appeal of topical formulations as they may impart an undesirable oily feel to the skin. By removing or significantly reducing the concentration of the occlusive agent, a decrease in the vasoconstrictor potency of the steroid would be expected. Thus, the effectiveness of the topical steroid formulation would be decreased.

The present fluticasone lotion invention unexpectedly shows increased vasoconstrictor potency of fluticasone at decreased concentrations of occlusive agent, thus increasing the steroid effectiveness. The instant fluticasone lotion also significantly improves the organoleptic feel and spreadability of the drug over a large area as compared to a cream. Specifically, the instant fluticasone lotion has improved vasoconstrictor activity over fluticasone cream formulations. The fluticasone lotion is systemically safe and exhibits significant vasoconstrictor potency and efficacy and excellent anti-inflammatory activity.

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SUMMARY OF THE INVENTION

One aspect of the invention is a topical lotion comprising about 0.005 to 1.0 wt.% fluticasone, or a pharmaceutically acceptable salt or ester thereof; a thickening effective concentration of at least one thickener; a conditioning effective concentration of at least one skin conditioning agent; and, an emulsifying effective amount of a surfactant. Unless indicated otherwise herein, all percentages are in terms of weight percent (i.e., w/w, wt.%, etc.). Unless indicated otherwise herein, the term "about" is intended to include values, e.g., weight percents, proximate to the recited range that are equivalent in terms of the functionality of the individual ingredient, the composition or the invention. In addition, unless indicated otherwise herein, a recited range (e.g., weight percents or carbon groups) includes each specific value or identity within the range.

Another aspect of the present invention is a topical fluticasone lotion for the treatment of skin conditions (i.e., dermatological disorders). The lotion comprises about 0.005 to 1.0 wt.% fluticasone, or a pharmaceutically acceptable salt or ester thereof; about 1.0 to 10.0 wt.% of a C_{14} - C_{20} fatty alcohol, or mixtures thereof; about 1.0 to 5.0 wt.% of at least one skin conditioning agent; about 5.0 to 15.0 wt.% of propylene glycol; up to about 10.0 wt.% mineral oil or soft white paraffin, and the balance being water. The lotion optionally contains additives such as preservatives and buffers.

Another aspect of the invention is a topical fluticasone lotion comprising fluticasone propionate in an amount of from about 0.005 to 1.0 wt.%; a C_{14} - C_{20} fatty alcohol, or mixtures thereof, in an amount of from about 3.0 to 7.0 wt.%; at least one skin conditioning agent in an amount of from about 0.5 to 3.0 wt.%; at least one surfactant in an amount of about 0.25 to 3.0 wt.%; propylene glycol in an amount of from about 7.0 to 12.0 wt.%; up to about 10 wt.% mineral oil or soft white paraffin; and the balance in water, preferably purified water, USP.

Yet another aspect of the invention is a method of treating a skin condition. A skin condition (or dermatological disorder) includes, but is not limited to, corticosteroid-responsive dermatosis, atropic dermatitis, inflammation, eczema, erythema, papulation, scaling, erosion, oozing, crusting and pruritis. The method comprises the

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steps or acts of providing a lotion including about 0.005 to 1.0 wt.% fluticasone, or a pharmaceutically acceptable salt or ester thereof; about 1.0 to 10.0 wt.% of a C₁₄-C₂₀ fatty alcohol or mixtures thereof; about 1.0 to 5.0 wt.% of one or more skin conditioning agents; about 5.0 to 15.0 wt.% of propylene glycol; up to about 10.0 wt.% of mineral oil or white soft paraffin, and the balance in purified water; and, applying the lotion to the skin having the skin condition. Preferably, the lotion has a 2-hour mean blanching score of at least about 2.1, an AUC of at least about 26.7, and an average mean blanching of at least about 1.5. The lotion of the present invention has the added benefit of being chemically and physically stable for at least 6 months at 40°C.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

Fluticasone or a pharmaceutically acceptable salt or ester thereof, preferably fluticasone proprionate, is present in the formulation in a concentration of from about 0.005 to 1.0 wt.% preferably 0.005 to 0.5 wt.%, and more preferably about 0.005 to about 0.1 wt.%. The C_{14} - C_{20} fatty alcohol or mixtures thereof are present in the formulation as a thickener and/or stabilizer. Examples include, but are not limited to, cetyl alcohol, stearyl alcohol, and cetostearyl alcohol. The C_{14} - C_{20} fatty alcohol is present in a concentration in the range of from about 1.0 to 10.0 wt.%, preferably about 3.0 to 7.0 wt.%, and more preferably about 4.0 to 6.0 wt.%.

Conventional skin conditioning agents, such as emollient skin conditioning agents, may be present in the lotion of the present invention. Skin conditioning agents are defined in the CTFA (Cosmetic Toiletry and Fragrance Association) Cosmetic Ingredient Handbook (2nd ed. 1992) and the Handbook of Pharmaceutical Excipients (2nd ed. 1994). Preferred examples of such skin conditioning agents include, but are not limited to, cholesterol, glycerine, glycerol monostearate, isopropyl myristate and palmitate, and lanolin alcohols, or mixtures thereof. Particular examples are isopropyl myristate and cetostearyl alcohol. The skin conditioning agent is present in a concentration in the range of from about 1.0 to 5.0 wt.%, preferably about 1.0 to 3.0 wt.%, and more preferably about 1.0 to 2.0 wt.%. In a preferred embodiment, dimethicone is employed in connection with at least one skin conditioning agent. The concentration of dimethicone in the formulation may be up to about 5.0 wt.%, preferably about 0.5 to 3.0 wt.% and more preferably about 1.0 to 2.0 wt.% of the lotion composition.

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At least one conventional surfactants may be used in topical formulations to form the oil-in-water emulsion lotion of the present invention. For example, the surfactants may include, but are not limited to, polyoxyalkene oxides of C_{14} - C_{20} fatty alcohols and polyoxyalkylene sorbitan esters, or mixtures thereof. Preferred surfactants include CETOMACROGOL® 1000 (Crodor Inc.), CETETH-20®, TWEEN® 40 or BRIG® 78. The surfactant may be present in a concentration in the range of about 0.25 to 3.0 wt.%, preferably about 0.5 to 2.0 wt.%, and more preferably about 0.75 to 1.5 wt.%.

Optionally, mineral oil or white soft paraffin are incorporated into the lotion in relatively small amounts to act as a skin conditioner. The lotion may also be free of mineral oil and/or white soft paraffin or contain up to about 10.0 wt.%. The lotion may also contain up to about 5.0 wt.% or up to about 2.0 wt.% skin conditioner.

Propylene glycol may be present in the lotion formulation in a concentration of from about 5.0 to 15.0 wt.%, preferably about 7.0 to 12.0 wt.% and more preferably 9.0 to 11.0 wt.%.

The viscosity of the fluticasone lotion may be in the range of about 2,000 to 17,000 centipoise (cps), and preferably about 3,000 to 13,000 cps, as measured by a Brookfield viscometer fitted with a #27 spindle at 10 rpm at 25°C.

The pH range of the topical fluticasone lotion may be in the range of about 4 to 7. Conventional buffers may be employed in the lotion formulation to achieve the pH range. The buffers include, but are not limited to, sodium citrate/citric acid, dibasic sodium phosphate/citric acid, and the like.

Optionally, conventional preservatives may be used in the present invention. Preferably, preservatives employed in the formulation should pass US Pharmacopoeia, British Pharmacopoeia and European Pharmacopoeia standards. Preferred preservatives include, but are not limited to, imidurea, methylparaben, propylparaben and the like, and combinations thereof.

Treatment of skin conditions with the lotion of the present invention is accomplished by applying the lotion to the affected areas to be treated. The treatment regimen is varied

from patient to patient and condition to condition. In general, the fluticasone lotion is to be applied once or twice a day to a treatment area. Preferably, the lotion of the present invention is used to treat atopic dermatitis, inflammatory and pruritic manifestations and corticosteroid-responsive dermatoses.

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The lotion of the present invention is manufactured in a conventional manner by mixing the ingredients at elevated temperatures (such as from 45-80°C) and then cooling the mixture to achieve a smooth, homogeneous oil-in-water emulsion.

The following examples merely illustrate the lotion compositions of the invention and are not to be construed as limiting the scope of the invention. Unless indicated otherwise, all weight percentages are based on the total weight of the composition.

EXAMPLES

Example 1

A topical 0.05 wt.% fluticasone propionate lotion in accordance with the present invention was prepared having the following composition.

20	Ingredient	<u>(wt.%)</u>
	Cetostearyl alcohol, NF	5.00
	Isopropyl myristate, NF	1.00
	Dimethicone 360, NF	1.00
	Cetomacrogol 1000, BP	1.00
25	Propylene glycol, USP	10.00
	Imidurea, NF	0.30
	Methyl paraben, USP	0.20
	Propyl paraben, USP	0.10
	Citric acid (anhydrous), USP	0.05
30	Sodium citrate, USP	0.08
	Purified water, USP	balance

A topical 0.05 wt.% fluticasone propionate lotion formulation in accordance with the present invention was prepared having the following composition.

5	Ingredient	(Wt.%)
	Cetostearyl alcohol, NF	5.25
	Isopropyl myristate, NF	2.00
	Propylene glycol, USP	0.00
A total de la companya de la company	Ceteth-20	0.75
<u>1</u> 10	Imidurea, NF	0.20
	Methyl paraben, USP	0.20
Section 2	Propyl paraben, USP	0.10
The state of the s	Citric Acid (anhydrous)	0.05
Transfer or Section 1997	Dibasic sodium phosphate	0.06
15	Purified water, USP	balance

Example 3

A topical fluticasone propionate lotion in accordance with the present invention was prepared having the following composition.

	• • • • • • • • • • • • • • • • • • • •	
	Ingredient	<u>(wt.%)</u>
	Fluticasone Propionate	0.05
	Cetosteoryl Alcohol	5.0
	Mineral Oil	3.0
25	Isopropyl myristate	3.0
	Ceteth-20	0.75
	Propylene Glycol	0.0
	Citric Acid (anhydrous)	0.05
	Dibasic Sodium Phosphate	0.06
30	Imidurea	0.20
	Water	balance

A topical fluticasone propionate lotion in accordance with the present invention was prepared having the following composition.

	-	
5	Ingredient	(<u>wt.%)</u>
	Fluticasone Propionate	0.05
	Cetosteoryl Alcohol	5.25
	Mineral Oil	1.0
or with the second seco	Isopropyl myristate	1.0
1 0	Ceteth-20	0.75
	Propylene Glycol	10.0
The state of the s	Citric Acid (anhydrous)	0.05
CONTROL OF THE CONTROL OF T	Dibasic Sodium Phosphate	0.06
	Imidurea	0.20
<u>1</u> 5	Water	balance

Example 5

A topical fluticasone propionate lotion in accordance with the present invention was prepared having the following composition.

	1	• •	
		Ingredient	<u>(wt.%)</u>
		Fluticasone Propionate	0.05
		Cetosteoryl Alcohol	5.0
		Mineral Oil	10.0
25		Isopropyl myristate	5.0
		Ceteth-20	0.75
		Propylene Glycol	10.0
		Citric Acid (anhydrous)	0.05
		Dibasic Sodium Phosphate	0.06
30		Imidurea	0.20
		Water	balance

A topical fluticasone propionate lotion in accordance with the present invention was prepared having the following composition.

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Ingredient	<u>(wt.%)</u>
Fluticasone Propionate	0.05
Cetosteoryl Alcohol	7.0
Isopropyl myristate	2.5
Dimethicone	2.5
Cetomacrogol 1000	1.0
Propylene Glycol	10.0
Citric Acid (anhydrous)	0.05
Sodium Citrate	0.075
Imidurea	0.30
Water	balance

Example 7

A topical fluticasone propionate lotion in accordance with the present invention was prepared having the following composition.

	Ingredient	(wt.%)
	Fluticasone Propionate	0.05
25	Cetosteoryl Alcohol	7.0
	Isopropyl myristate	5.0
	Dimethicone	2.5
	Cetomacrogol 1000	1.0
	Propylene Glycol	10.0
30	Citric Acid (anhydrous)	0.05
	Sodium Citrate	0.075
	Imidurea	0.30
	Water	balance

A topical fluticasone propionate lotion in accordance with the present invention was prepared having the following composition.

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	Ingredient	(wt.%)
	Fluticasone Propionate	0.05
	Cetosteoryl Alcohol	6.0
	Isopropyl myristate	2.0
_10	Cetomacrogol 1000	1.0
organical and service and serv	Propylene Glycol	10.0
Secretary of the secret	Citric Acid (anhydrous)	0.05
The part of the control of the contr	Sodium Citrate	0.075
	Imidurea	0.30
15	Water	balance
	Example 9	
Transfer on the control of the contr	A topical fluticasone propionate lotion in accord	ance with the
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Example 9

A topical fluticasone propionate lotion in accordance with the present invention was prepared having the following composition.

	Ingredient	<u>(wt.%)</u>
	Fluticasone Propionate	0.05
	Cetosteoryl Alcohol	4.7
25	Isopropyl myristate	3.75
	Dimethicone	3.75
	Cetomacrogol 1000	1.0
	Propylene Glycol	10.0
	Citric Acid (anhydrous)	0.05
30	Sodium Citrate	0.075
	lmidurea	0.30
	Water	balance

Example 10

A topical fluticasone propionate lotion in accordance with the present invention was prepared having the following composition.

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	Ingredient	<u>(wt.%)</u>
	Fluticasone Propionate	0.05
	Cetosteoryl Alcohol	2.4
	Isopropyl myristate	2.5
0	Dimethicone	5.0
	Cetomacrogol 1000	1.0
	Propylene Glycol	10.0
	Citric Acid (anhydrous)	0.05
	Sodium Citrate	0.075
5	Imidurea	0.30
	Water	balance

Example 11

A topical fluticasone propionate lotion in accordance with the present invention is prepared having the following composition.

	Ingredient	(wt.%)
	Fluticasone Propionate	0.01
25	Stearyl Alcohol	5.0
	Isopropyl myristate	3.0
	Dimethicone	3.0
	Ceteth-20	0.75
	Propylene Glycol	5.0
30	Imidurea, NF	0.20
	Methyl paraben, USP	0.20
	Propyl paraben, USP	0.10
	Water	balance

PCT/GB99/03472

Example 12

A topical fluticasone propionate lotion in accordance with the present invention was prepared having the following composition.

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Li
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Ingredient	<u>(wt.%)</u>
Fluticasone Propionate	0.01
Stearyl Alcohol	2.5
Mineral Oil	1.0
Isopropyl myristate	1.0
Dimethicone	1.0
Cetomacrogol 1000	0.5
Propylene Glycol	15.0
Imidurea, NF	0.20
Methyl paraben, USP	0.20
Propyl paraben, USP	0.10
Water	balance

Example 13

A topical fluticasone propionate lotion in accordance with the present invention was prepared having the following composition.

	Ingredient	(wt.%)
25	Fluticasone Propionate	0.1
	Cetyl Alcohol	7.0
	Mineral Oil	2.0
	Isopropyl myristate	2.0
	Dimethicone	2.0
30	Cetomacrogol 1000	1.5
	Propylene Glycol	10.0
	Imidurea, NF	0.20
	Methyl paraben, USP	0.20
	Propyl paraben, USP	0.10
35	Water	balance

A topical fluticasone propionate lotion in accordance with the present invention was 5 prepared having the following composition.

	Ingredient	<u>(wt.%)</u>
	Fluticasone Propionate	0.1
	Stearyl Alcohol	7.0
<u></u>	Mineral Oil	2.5
TO THE PARTY OF TH	Dimethicone	2.5
	Ceteth-20	1.0
James Andrews	Propylene Glycol	15.0
Frank SF A ST A	Imidurea, NF	0.20
15	Methyl paraben, USP	0.20
25	Propyl paraben, USP	0.10
The Ample of the Control of the Cont	Water	balance
500 0 0 0 0 0 0 0 0 0 0 0 0 0		
Appears in a comment of the comment	Example 1	<u>15</u>
v		

Example 15

A topical fluticasone propionate lotion in accordance with the present invention was prepared having the following composition.

	Ingredient	(wt.%)
25	Fluticasone Propionate	0.1
	Cetostearyl Alcohol	5.0
	Mineral Oil	2.5
	Dimethicone	1.0
	Tween®40	0.5
30	Propylene Glycol	10.0
	Imidurea, NF	0.20
	Methyl paraben, USP	0.20
	Propyl paraben, USP	0.10
	Water	balance

A topical fluticasone propionate lotion in accordance with the present invention was prepared having the following composition.

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	Ingredient	<u>(wt.%)</u>
	Fluticasone Propionate	0.1
	Stearyl Alcohol	5.25
	Mineral Oil	5.0
10	Brig®78	2.0
of the second se	Propylene Glycol	5.0
A CONTROL OF THE CONT	Imidurea, NF	0.20
10 11 11 15	Methyl paraben, USP	0.20
Exception on the second of the	Propyl paraben, USP	0.10
15	Water	balance
or and the control of		
Committee Commit	Example 17	
20 1000 00 00 00 00 00 00 00 00 00 00 00		
Comments of	A topical fluticasone propionate lotion in accord	ance with the
20	prepared having the following composition.	

Example 17

A topical fluticasone propionate lotion in accordance with the present invention was prepared having the following composition.

	Ingredient	(wt.%)
	Fluticasone Propionate	0.05
	Cetyl Alcohol	2.0
25	Isopropyl myristate	5.0
	Cetomacrogol 1000	0.5
	Propylene Glycol	10.0
	Imidurea, NF	0.20
	Methyl paraben, USP	0.20
30	Propyl paraben, USP	0.10
	Water	balance

A topical fluticasone propionate lotion in accordance with the present invention was prepared having the following composition.

d	1		
4		١	
		,	

	Ingredient	<u>(wt.%)</u>
	Fluticasone Propionate	0.05
	Cetyl Alcohol	2.5
	Dimethicone	5.0
_ 10	Cetomacrogol 1000	1.0
100 to 10	Propylene Glycol	10.0
2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2	lmidurea, NF	0.20
Transfer, or	Methyl paraben, USP	0.20
	Propyl paraben, USP	0.10
15	Water	balance
of the control of the		
# = 20	The topical anti-inflammatory activity of fluti measured using a vasoconstriction assay (McK 86, 608(1962)).	

The topical anti-inflammatory activity of fluticasone propionate formulations was measured using a vasoconstriction assay (McKenzie and Stoughton, Arch. Dermatol., 86, 608(1962)).

Approximately 0.1 mL of the drug product of Examples 1-18 were placed on a 2 cm² area of the volar aspect of each volunteer's forearm. Application sites were protected with a guard to prevent removal or smearing. The application sites were not occluded. After approximately 16 hours of contact, the protective guards were removed and the sites gently washed and dried.

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Skin vasoconstrictor evaluations were preformed on a 4 point scale (0 [no blanching]-3[marked blanching]) at time points corresponding to 2, 3, 6, 8, and 24 hours after drug removal. The data were used to calculate the mean blanching response and the area under the curve (AUC) for the blanching versus time. The higher the score, mean or area under the curve (AUC), the more topically potent. The results are tabulated in Table 1.

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Table 1

Measure*	Lotion Example 1	Lotion Example 2	CUTIVATE® (Fluticasone proprionate) Cream Comparative Example
AUC	28.4	26.7	21.4
Mean	1.58	1.49	1.22

^{*}Results from 17 volunteers.

The fluticasone lotions of the present invention show higher vasoconstriction scores than fluticasone cream. As shown by the 17 patient data set, the vasoconstriction potency of the fluticasone lotions is greater than the cream.

The fluticasone lotion of the present invention has proven to be unexpectedly superior in terms of efficacy and safety. Evaluations were performed using the Vasoconstrictor Assay. Evaluations also used a human model to predict clinical potency of corticosteroids in (1) controlled efficacy and safety trials and (2) subjects with a corticosteroid-responsive dermatosis, atopic dermatitis. Safety and efficacy evaluations were performed on the fluticasone lotion 0.05% by applying the lotion extensively to all body regions: head and neck (including face), trunk, upper limbs and lower limbs.

The potency of the fluticasone lotion, as determined by the Vasoconstrictor Assay, was greater than mid-potency fluticasone cream (CUTIVATE™ Cream). The potency of the fluticasone lotion was less than the high-potency corticosteroid preparations. Application of the lotion formulation over 4 weeks resulted in a superior adverse event profile devoid of commonly encountered side effects encountered using corticosteroids in the mid-to-high potency range.

The instant fluticasone lotion was assessed in view of projected efficacy outcomes from the Vasoconstrictor Assay (VC Assay) in humans and corroborated by efficacy outcomes in multicenter vehicle-controlled clinical trials. It was highly desirable for the lotion formulation to show both systemic (adrenal axis suppression) and local (atrophogenic) responses to corticosteroids. The fluticasone lotion was unexpectedly

superior in both categories, and particularly superior in that no atrophy was observed (based on associated signs) even in the more susceptible region (i.e., the face, head and neck).

The Vasoconstrictor Assay (VC Assay; McKenzie and Stoughton) is a standard dermatological assay used to predict the potency of corticosteroid formulations. Potency is related to both side effect potential and efficacy in the treatment of mild to severe dermatoses. Reactions of particular concern include skin thinning (atrophy, including telangectasia), and adrenal axis suppression, which can occur more often (1) under occlusions or (2) when higher potency corticosteroids are employed.

In the VC assay, fluticasone lotion 0.05% was compared to low-potency (HYTONE™ Lotion), mid-potency (CUTIVATE™ Cream; and fluticasone cream 0.05%) and high-potency (TEMOVATE™ Cream; ELOCON™ Lotion). Potency was estimated for two subject populations (Intent to Treat and Positive responders) and includes 3 outcome assessments: 2-hour mean blanching score, are under the time-blanching score curve (AUC) and Average mean blanching from 5 timepoints. The results from the "responder" population is summarised in Table 2.

Table 2

Treatment	Potency	Responder Population				
		2 hour score	2 hour score AUC A			
				blanching		
TEMOVATE™	High	2.7	36.6	2.0		
ELOCON™	High	2.2	33.4	1.8		
Fluticasone	Mid to High	2.1	26.7	1.5		
lotion (0.05%)						
CUTIVATE™	Mid	1.8	21.4	1.2		
Cream						
HYTONE™	Low	0.8	9.5	0.6		
Lotion						

The results show that the fluticasone lotion of the present invention has an unexpectedly high potency for a lotion-based composition.

In addition, as shown in Table 3, criticality for the presence of fluticasone in the lotion of the present invention was established by the comparison between applying the vehicle alone (the fluticasone lotion minus the fluticasone propionate) and the fluticasone lotion. The FPL10005, FPL3003 and FPL30004 studies used the following fluticasone 0.05% lotion formulation.

	Ingredient	(wt.%)
	fluticasone propionate (micronized)	0.05
10	cetostearyl alcohol, NF	5.0
	isopropyl myristate, NF	1.0
2	dimethicone 360, NF	1.0
Control Sept. Anagoning of a control of the contro	polyoxyethylene (20) cetostearyl ether, NF	1.0
A SECOND FOR	propylene glycol, USP	10.0
15	imidurea, NF	0.14
Single State of the State of th	methylparaben, NF	0.17
Manager And Chingdon And Chingdon And Sange An	propylparaben, NF	0.06
5 E E E E E E E E E E E E E E E E E E E	citric acid (hydrous), USP	0.05
ATTACHER TO A STATE OF THE STAT	sodium citrate, USP	0.08
20	purified water, USP	balance (also QSAD)

Table 3

Study	Diagnosis	Application	No. subjects	Outcome
				Good to
1				cleared(%)
FPL30003	Atopic	QD for up to	FPL (110)	FPL (78%)*
	Dermatitis	4 weeks	Veh. (110)	Veh. (33%)
FPL30004	Atopic	QD for up to	FPL (111)	FPL (68%)
	Dermatitis	4 weeks	Veh. (107)	Veh. (28%)

^{*} subjects showing > 50% clearing of lesions

[&]quot;Veh." is vehicle only formulation

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The data of Table 3 show that the fluticasone lotion is more than twice as effective as the vehicle. In a once-a-day application, the differences (%) between the vehicle-only and the fluticasone lotion are 40% and 45% (FPL30004 and FPL30003, respectively). The advantage of the fluticasone propionate lotion over the vehicle control was unexpectedly superior. It is worth noting that the fluticasone lotion application rate was half the preferred application rate of twice per day.

Systemic safety of fluticasone lotion (study FPL10005) was assessed utilising the measurement of adrenal responsiveness to a challenge of cosyntropin (ACTH₁₋₂₉) and measuring the plasma levels of cortisol both before and 30 minutes after ACTH challenge. HPA axis was considered suppressed if the cortisol response to the challenge was less than 18 ug/dL. These studies were conducted in paediatric populations from 3 months to 5 years of age. Because children have a high ratio of body mass to surface, that population is considered to be more at risk than adults.

In these studies fluticasone formulations were tested following a 3 or 4 week course of twice daily application of the fluticasone lotion to at least 35% of the body surface area in subjects with moderate to severe eczema. The results are summarised in Table 4.

Table 4

Cortisol responses - plasma levels =18 ug/dL indicate suppression

Obition Copolicoo pidoma is	10.0	
Study	Preparation	Adrenal
		Responsiveness,
		#suppressed/total
FPL10005	Lotion	0 / 42

These data show that the fluticasone lotion did not suppress the adrenal responsiveness to ACTH stimulation. CUTIVATE™ lotion produced low adrenal suppression as evaluated by the cosyntropin (ACTH₁₋₂₉) stimulation test in paediatric subjects. This age group would be expected to be the most susceptible to side effects of corticosteroids. No adrenal suppression was noted for CUTIVATE™ lotion. These results were unexpectedly superior based on potency estimates from the VC

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Assay.

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Treating skin diseases with topical corticosteroids is of particular concern where the skin is thin (e.g., the face) due to the potential atrophy side effect. Skin atrophy and atrophy-associated signs (such as telangectasia) were monitored in safety studies (HPA Axis Suppression) and efficacy (multicenter pivotal trials). The fluticasone lotion showed no atrophy-associated changes (see Table 4). In addition, atrophogenic potential was assessed in two large multicenter trials (FPL30003, N= 110 treated with fluticasone); FPL30004; N= 111 treated with fluticasone). The subjects had moderate-to-severe atopic dermatitis. After once daily administration for up to 4 weeks, no atrophy or associated signs were ascribed to drug treatment.

Based on the observed outcomes in the VC Assay (used to predict clinical potency), it was expected (1) that the therapeutic benefit would be only slightly more than that for CUTIVATETM Cream and (2) that the side effects would reflect those observed for CUTIVATETM Cream. The results were unexpected in that the lotion formulation was more effective than, and superior to, the cream. At half the application rate of fluticasone lotion, a lack of side effects were observed. That observation was unexpected since application of steroids of similar potency typically cause some side effects. As noted herein for the lotion, the lack of both systemic (HPA Axis suppression) and local side effects, even to sensitive areas such as the face (head and neck region) was unexpected.

It will be apparent to those skilled in the art that many modifications and equivalents thereof may be made without departing from the spirit and scope of the invention as set forth in the appended claims.

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1. A topical lotion comprising:

about 0.005 to 1.0 wt.% fluticasone, or a pharmaceutically acceptable salt or ester thereof;

about 1.0 to 10.0 wt.% of a C₁₄-C₂₀ fatty alcohol or mixtures thereof;

about 1.0 to 5.0 wt.% of at least one skin conditioning agent;

about 5.0 to 15.0 wt.% propylene glycol;

up to about 10.0 wt.% mineral oil or white soft paraffin; and

the balance in water.

2. A topical lotion comprising:

about 0.005 to 1.0 wt.% fluticasone propionate;

about 3.0 to 7.0 wt.% of a C₁₄-C₂₀ fatty alcohol, or mixtures thereof;

about 0.5 to 3.0 wt.% of at least one skin conditioning agent;

about 0.25 to 2.0 wt.% of at least one surfactant;

about 7.0 to 12.0 wt.% propylene glycol;

up to about 10 wt.% of mineral oil or white soft paraffin; and

the balance in water.

- 3. The lotion according to claim 1, further comprising less than about 5.0 wt.% dimethicone.
- 4. The lotion according to claim 2, further comprising less than about 5.0 wt.% 25 dimethicone.
 - 5. The lotion according to claim 1, wherein said pharmaceutically acceptable ester of fluticasone is fluticasone propionate.
- 30 6. The lotion according to claim 1, comprising:

about 0.05 wt.% fluticasone propionate,

about 5.0 wt.% cetostearyl alcohol,

about 1.0 wt.% isopropyl myristate,

about 1.0 wt.% dimethicone,

35 about 1.0 wt.% cetomacrogol,

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about 10.0 wt.% propylene glycol
less than about 0.30 wt.% imidurea,
less than about 0.20 wt.% methyl paraben,
less than about 0.10 wt.% propyl paraben,
about 0.05 wt.% citric acid (anhydrous),
about 0.08 wt.% sodium citrate, and
the balance in purified water.

- 7. The lotion according to claim 1, comprising: about 0.05 wt.% fluticasone propionate, about 5.25 wt.% cetostearyl alcohol, about 2.0 wt.% isopropyl myristate, about 10.0 wt.% propylene glycol, about 0.20 wt.% imidurea, about 0.20 wt.% methyl paraben, about 0.10 wt.% propyl paraben, and the balance in purified water.
- 8. The lotion according to claim 1, having a viscosity of about 2,000 to 17,000 cps as measured by a Brookfield viscometer fitted with a #27 spindle at 10 rpm at 25°C.
- The lotion according to claim 2, having the formula about 5.25 wt.% cetostearyl alcohol, about 2.0 wt.% isopropyl myristate,
 about 10.0 wt.% propylene glycol, about 0.20 wt.% imidurea, about 0.20 wt.% methyl paraben, about 0.10 wt.% propyl paraben, and the balance in purified water.

10. The lotion according to claim 1, having a viscosity of from about 3,000 to 13,000 cps as measured by a Brookfield viscometer fitted with a #27 spindle at 10 rpm at 25°C

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- 11. The lotion according to claim 2, having a viscosity of from about 3,000 to 13,000 cps as measured by a Brookfield viscometer fitted with a #27 spindle at 10 rpm at 25°C.
- 5 12. The lotion according to claim 1, free of mineral oil or white soft paraffin.
 - 13. The lotion according to claim 2, free of mineral oil or white soft paraffin.
 - 14. Use of the lotion according to claim 1 to increase the vasoconstrictor potency of fluticasone.
 - 15. Use of the lotion according to claim 2 to increase the vasoconstrictor potency of fluticasone proprionate.
 - 16. A process for preparing a lotion according to claim 1, comprising: mixing the ingredients recited in claim 1 at an elevated temperature; and cooling said mixture.
 - 17. A process for preparing a lotion according to claim 1, comprising: mixing the ingredients recited in claim 1 at an elevated temperature; and heating said mixture.
 - 18. A topical lotion comprising:
 - about 0.005 to about 1.0 wt.% fluticasone, or a pharmaceutically acceptable salt or ester thereof;
 - a thickening effective concentration of at least one thickener; a conditioning effective concentration of at least one skin conditioning agent; an emulsifying effective amount of a surfactant, and the balance in water.
 - 19. The lotion of claim 18, wherein the lotion has a 2-hour mean blanching score of at least about 2.1, an AUC of at least about 26.7, and an average mean blanching of at least about 1.5.

- 20. The lotion of claim 18, wherein the lotion is chemically and physically stable for at least 6 months at 40°C.
- 21. A method of treating a skin condition comprising:
- providing a lotion including about 0.005 to about 1.0 wt.% fluticasone, or a pharmaceutically acceptable salt or ester thereof; about 1.0 to about 10.0 wt.% of a C₁₄-C₂₀ fatty alcohol or mixtures thereof; about 1.0 to about 5.0 wt.% of at least one skin conditioning agents; about 5.0 to about 15.0 wt.% of propylene glycol; less than about 10.0 wt.% of mineral oil or white soft paraffin, and the balance in water; and, applying the lotion to the skin having the skin condition.
 - 22. The method of claim 21, wherein the skin condition is corticosteroid-responsive dermatosis, atopic dermatitis, inflammation, eczema, erythema, papulation, scaling, erosion, oozing, crusting or pruritis.
 - 23. The topical lotion of claim 21, wherein the lotion has a 2-hour mean blanching score of at least about 2.1, an AUC of at least about 26.7, and an average mean blanching of at least about 1.5.
 - 24. The lotion of claim 21, wherein the lotion is chemically and physically stable for at least 6 months at 40°C.

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POWER the U.S. P	OF ATTORNEY: A	s a named inventor, I hereby appoint the fo Office connected therewith. (List name an	ollowi nd regi	ng attorney(s) stration numb	and/or agent(s) to proser)	secute this application a	nd transact all business in
David J. Levy Reg. No. 27,655 Charles E. Dadswell Reg. No. 35,851 Karen L. Prus Reg. No. 39,337 Robert H. Brink Reg. No. 36,094 Elizabeth Selby Reg. No. 38,298			James P. Riek Reg. No. 39,009 Bonnie L. Deppenbrock Reg. Virginia C. Bennett Reg. No. 37,092 John L. Lemanowicz Reg. No. 31,164 Christopher P. Rogers Reg. No. 38,181				
Send Co	orrespondence to:				i i ilii i iii i ii ii ii ii ii ii ii ii	Direct Telephone Ca	alls to
Same of	David J. Levy, Pate					Christon	her P. Rogers
Aleste for	Global Intellectual Glaxo Wellcome In	Property Department		23	347		483-1240
Five Moore Drive, PO Box 13398 PATENT TRADEMARK OFFICE					DEMARK OFFICE		
7-1-1-1-1-1-1-1-1-1-1-1-1-1-1-1-1-1-1-1	Research Triangle						
s							
	and belief are be	that all statements made herein of lieved to be true; and further that the he like so made are punishable by	these	statements	were made with th	e knowledge that v	villful false
	willful false state	ements may jeopardize the validity	y of tl	he applicati	on or any patent is	suing thereon.	
	FULL NAME	FAMILY NAME		RST GIVEN NAM	Œ	SECOND GIVEN NAME	Z/INITIAL
2==	OF INVENTOR	DOW	G	ordon		J.	
	INVENTOR'S SIGNATURE						
0	RESIDENCE &	СПУ	-	STATE OR FOI	REIGN COUNTRY	COUNTRY OF CITIZES	NSHIP
	CITIZENSHIP *	Petaluma		CA		US	
_	POST OFFICE	POST OFFICE ADDRESS		CITY Petaluma		STATE & ZIP CODE/COUNTRY CA 94954, US	
1	ADDRESS	Dow Pharmaceutical Science 1330A Redwoodway		гетанина		CA 94934, US	
	FULL NAME	FAMILY NAME		FIRST GIVEN	NAME	SECOND GIVEN NAMI	E/INITIAL
2	OF INVENTOR	JOHNSON		Keith		Arthur	
	INVENTOR'S SIGNATURE						
0	RESIDENCE &	СПУ		ATE OR FOREIG	GN COUNTRY	COUNTRY OF CITIZE	NSHIP
	CITIZENSHIP	Durham	N			STATE & ZIP CODE/C	OVINTEN
2	POST OFFICE ADDRESS	POST OFFICE ADDRESS GlaxoSmithKline		Research	Triangle Park	NC 27709, US	JUNIKI
	ADDRESS	Five Moore Drive, PO Box 13398				1, 55	
,	FULL NAME	FAMILY NAME		RST GIVEN NAM	1E	SECOND GIVEN NAME	E/INITIAL
200	OF INVENTOR	KELLY	<u>F</u>	rances	1	Furr	
p -	INVENTOR'S SIGNATURE	Mames Tur	1 -	1000		1 X April 1	8, 2001
0	RESIDENCE &	CITY		ATE OR FOREI	COUNTRY	COUNTRY OF CITIZE	4
	CITIZENSHIP	Ducham POST OFFICE ADDRESS	N	C A	10	STATE & ZIP CODE/C	OUNTRY
3	POST OFFICE ADDRESS	GlaxoSmithKline			/ riangle Park	NC 27709, US	COMINE
١		Five Moore Drive, PO Box 13398	1		8	1	

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	COMBINED DECLARATION FOR UTILITY or DESIGN ATTORNEY'S DOCKET NUMBER PU3556USW								
PAT	PATENT APPLICATION WITH POWER OF ATTORNEY Continued								
V 12/2/	FULL NAME OF INVENTOR	FAMILY NAME LATHROP	FIRST GIVEN NAME Robert	SECOND GIVEN NAME/INITIAL William					
fee .	INVENTOR'S SIGNATURE	Lattery	Figure STATE OR FOREIGN COUNTRY	COUNTRY OF CITIZENSHIP					
0	RESIDENCE & CITIZENSHIP	Fort Collins	US STATE & ZIP CODE/COUNTRY						
4	POST OFFICE ADDRESS	POST OFFICE ADDRESS GlaxoSmithKline Five Moore Drive, PO Box 13398	Research Triangle Park	NC 27709, US					
2	FULL NAME OF INVENTOR	FAMILY NAME RAJAGOPALAN	FIRST GIVEN NAME Rukmini	SECOND GIVEN NAME/INITIAL					
	INVENTOR'S SIGNATURE			COUNTRY OF CITIZENSHIP					
0	RESIDENCE & CITIZENSHIP	Durham	NC US						
5	POST OFFICE ADDRESS	POST OFFICE ADDRESS GlaxoSmithKline Five Moore Drive, PO Box 13398	Research Triangle Park	NC 27709, US					

DECLARATION FOR "371" APPLICATION

_	ATTORNEY'S DOCKET NUMBER								
	COMBINED DECLARATION FOR UTILITY or DESIGN ATTORIES BUCKET NORMER PU3556USW								
	PATENT APPLICATION WITH POWER OF ATTORNEY Continued								
H		FULL NAME	FAMILY NAME	THOSE GIVEN THE PERSON	SECOND GIVEN NAME/INITIAL				
ı	2	OF INVENTOR	LATHROP	Robert	William				
1	Ì	INVENTOR'S							
Т		SIGNATURE							
1	0	RESIDENCE &	CITY	STATE OR TOREIGN COUNTY	COUNTRY OF CITIZENSHIP				
١	Š	CITIZENSHIP	Fort Collins	CO	US				
ı	1	POST OFFICE	POST OFFICE ADDRESS	CILI	STATE & ZIP CODE/COUNTRY				
1	4	ADDRESS	GlaxoSmithKline	Research Triangle Park	NC 27709, US				
١			Five Moore Drive, PO Box 13398						
h		FULL NAME	FAMILY NAME	FIRST GIVEN NAME	SECOND GIVEN NAME/INITIAL				
l	.2)	OF INVENTOR	RAJAGOPALAN	Rukmini					
F	jtê)	INVENTOR'S	Kajagopalem		X10APR2001				
ナ	<i>'</i>	SIGNATURE	Kayagopalem	•					
Ţ	0	RESIDENCE &	CITY	STATE OR FOREIGN COUNTRY	COUNTRY OF CITIZENSHIP				
١	-	CITIZENSHIP	D <u>urham</u>	NC /V	US				
-		POST OFFICE	POST OFFICE ADDRESS	CITY	STATE & ZIP CODE/COUNTRY				
l	5	ADDRESS	GlaxoSmithKline	Research Triangle Park	NC 27709, US				
			Five Moore Drive, PO Box 13398	1					

	COMBINED DECLARATION FOR UTILITY OR DESIGN PATENT APPLICATION WITH POWER OF ATTORNEY						
(X) Decl	X) Declaration submitted with initial filing or						
()Decla)Declaration submitted after initial filing (surcharge required 37CFR1.16(e))						
	As below named	inventor. I hereby declare that:					
	My residence, post office a	address and citizenship are as stated belo	ow next to my name.				
	I believe I am the original, (if plural names are listed) entitled:	first and sole inventor (if only one name below) of the subject matter which is cla	e is listed below) or an original, the common timed and for which a patent is so	first and joint inventor ought on the invention			
		SONE LOTION HAVING IMPROVE (check only one item below):	ED VASOCONSTRICTOR AC	TIVITY			
	[]is attached hereto. OR						
Harry day	[x] was filed on 20 Octo	ber 1999 as United States application S	derial No or PC	'I International			
	Application Number PCT applicable)	C/GB99/03472 filed and was amended o	n (MM/DD/YYYY)	(if			
Ti Mi Mi	I hereby state that I have r as amended by any amend	eviewed and understand the contents of ment specifically referred to above.	the above-identified specification	n, including the claims,			
1000 ji 1000 la	I acknowledge the duty to	disclose information which is material t	to patentability as defined in 37 (CFR §1.56.			
	or inventor's certificate or United States of America,	ority benefits under 35, U.S.C. §119 (a)-365(a) of any PCT international applica listed below and have also identified be cate or of any PCT international applica	tion which designated at least on low, by checking the box, any for	ne country other than the breign application for			
1	The state of the s	RIORITY CLAIMS UNDER 35 U.S.C		PRIORITY			
Prio	r Foreign Application Number (s)	Country	Foreign Filing Date (MM/DD/YYYY))	CLAIMED			
1. 982	3036.0	GB	22 October 1998	X			
2.							
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5.	5.						
I hereb	·	tle 35, United States Code §119(e) of ar		ication(s) listed below:			
1	Application No.	Filing Date	e (MM/DD/YYYY)				
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COM	COMBINED DECLARATION FOR UTILITY or DESIGN ATTORNEY'S DOCKET NUMBER PU3556USW								
PAT	PATENT APPLICATION WITH POWER OF ATTORNEY Continued								
	FULL NAME	FAMILY NAME	FIRST GIVEN NAME	SECOND GIVEN NAME/INITIAL					
2	OF INVENTOR	LATHROP	Robert	William					
	INVENTOR'S								
ſ	SIGNATURE								
0	RESIDENCE &	CITY	STATE OR FOREIGN COUNTRY	COUNTRY OF CITIZENSHIP					
1	CITIZENSHIP	Fort Collins	CO	US					
l	POST OFFICE	POST OFFICE ADDRESS	CITY	STATE & ZIP CODE/COUNTRY					
4	ADDRESS	GlaxoSmithKline	Research Triangle Park	NC 27709, US					
Ì	1	Five Moore Drive, PO Box 13398	}						
	FULL NAME	FAMILY NAME	FIRST GIVEN NAME	SECOND GIVEN NAME/INITIAL					
2	OF INVENTOR	RAJAGOPALAN	Rukmini						
l	INVENTOR'S								
	SIGNATURE	1							
0	RESIDENCE &	CITY	STATE OR FOREIGN COUNTRY	CC. INTRY OF CITIZENSHIP					
	CITIZENSHIP	Durham	NC_	US					
Ì	POST OFFICE	POST OFFICE ADDRESS	CITY	STATE & ZIP CODE/COUNTRY					
5	ADDRESS	GlaxoSmithKline	Research Triangle Park	NC 27709, US					
[Five Moore Drive, PO Box 13398								

APPI	IBINED DECLAR LICATION WITH laration submitted with initial aration submitted after initial fi	POWER O	F ATTORNEY	R DESIGN PATENT	PU3556 First Name Gordon	es Inventor: J. DOW Se if known: : ate	
	As below named	inventor. I hereby	declare that:				
	My residence, post office	address and citizer	nship are as stated bel	ow next to my name.			
	My residence, post office address and citizenship are as stated below next to my name. I believe I em the original, first and sole inventor (if only one name is listed below) or an maiginal, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled: FLUTICASONE LOTION HAVING IMPROVED VASOCONSTRICTOR ACTIVITY the specification of which (check only one item below): [] is attached hereto. OR [x] was filed on 20 October 1999 as United States application Serial No or PCT International Application Number PCT/GB99/03472 filed and was amended on (MM/DD/YYYY) (if applicable) I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment specifically referred to above. I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR §1.56. I hereby claim foreign priority benefits under 35, U.S.C. §119 (a)-(d) or §365(b) of any foreign applications(s) for patent or inventor's certificate or 365(a) of any PCT international application which designated at least one country other than the United States of America, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate or of any PCT international application having a filing date before that of the application on						
t	r Foreign Application		MS UNDER 35 U.S. ountry	C. 119: Foreign Filing Date		PRIORITY	
	Number (s)			(MM/DD/YYYY))		CLAIMED	
	3036.0		GB	22 October 1998		X	
2. 3. 4. 5. I hereb	y claim the benefit under T Application No.	itle 35, United Sta		ny United States provisional appl te (MM/DD/YYYY)	ication(s)	listed below:	
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COM	COMBINED DECLARATION FOR UTILITY or DESIGN ATTORNEY'S DOCKET NUMBER PU3556USW								
PAT	PATENT APPLICATION WITH POWER OF ATTORNEY Continued								
	FULL NAME FAMILY NAME FIRST GIVEN NAME SECOND GIVEN NAME/INITIAL								
2	OF INVENTOR	LATHROP	Robert	William					
i	INVENTOR'S								
}	SIGNATURE		STATE OR FOREIGN COUNTRY	COUNTRY OF CITIZENSHIP					
0	RESIDENCE &	CITY	CO	US					
	CITIZENSHIP	Fort Collins		STATE & ZIP CODE/COUNTRY					
Ì	POST OFFICE	POST OFFICE ADDRESS	CITY David	NC 27709, US					
4	ADDRESS	GlaxoSmithKline	Research Triangle Park	NC 27709, US					
		Five Moore Drive, PO Box 13398							
	FULL NAME	FAMILY NAME	FIRST GIVEN NAME	SECOND GIVEN NAME/INITIAL					
2	OF INVENTOR	RAJAGOPALAN	Rukmini						
	INVENTOR'S			Į.					
	SIGNATURE			COUNTRY OF CITIZENSHIP					
0	RESIDENCE &	CITY	STATE OR FOREIGN COUNTRY	US					
1	CITIZENSHIP	Durham	NC						
i	POST OFFICE	POST OFFICE ADDRESS	CITY	STATE & ZIP CODE/COUNTRY					
5 ADDRESS GlaxoSmithKline Research Triangle Park NC 27709, U			NC 27/09, US						
	1	Five Moore Drive, PO Box 13398	1						

COMBINED DECLARATION FOR UTILITY OR DESIGN PATENT APPLICATION WITH POWER OF ATTORNEY						EY'S DOCKET 6USW les Inventor:	
ALL!	ATTEMENTATION WITH TOWNER OF ATTORNET						
	(X) Declaration submitted with initial filing or ()Declaration submitted after initial filing (surcharge required 37CFR1.16(e))						
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					Group A	Art Unit:	
	As below named	l inventor. I here	by declare that:				
İ	My residence, post office	address and citiz	zenship are as stated belo	ow next to my name.			
				e is listed below) or an original, a simed and for which a patent is so			
	FLUTICA the specification of which			ED VASOCONSTRICTOR AC	TIVITY		
	[]is attached hereto. OR						
7.5 58 58	[x] was filed on 20 October 1999 as United States application Serial No or PCT International						
Marie Constitution of the	Application Number PC applicable)	T/GB99/03472 f	iled_and was amended o	n (MM/DD/YYYY)		_(if	
United to	I hereby state that I have as amended by any amen			the above-identified specification	n, includii	ng the claims,	
	I acknowledge the duty to	o disclose inform	ation which is material t	to patentability as defined in 37 C	FR §1.56	j.	
	I hereby claim foreign priority benefits under 35, U.S.C. §119 (a)-(d) or §365(b) of any foreign applications(s) for patent or inventor's certificate or 365(a) of any PCT international application which designated at least one country other than the United States of America, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate or of any PCT international application having a filing date before that of the application on which priority is claimed:						
	R FOREIGN AND ANY P					DDIODZZY	
Prio	r Foreign Application Number (s)	(Country	Foreign Filing Date (MM/DD/YYYY))	,	PRIORITY CLAIMED	
1. 982			GB	22 October 1998		X	
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3. 4.							
5.						<u> </u>	
	y claim the benefit under T	itle 35, United St	tates Code §119(e) of an	l y United States provisional appli	ication(s)	listed below:	
	Application No.			e (MM/DD/YYYY)			
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CON	COMBINED DECLARATION FOR UTILITY or DESIGN ATTORNEY'S DOCKET NUMBER PU3556USW ATTORNEY'S DOCKET NUMBER PU3556USW								
PAT	PATENT APPLICATION WITH POWER OF ATTORNEY Continued								
2	FULL NAME OF INVENTOR	FAMILY NAME LATHROP	FIRST GIVEN NAME Robert	SECOND GIVEN NAME/INITIAL William					
	INVENTOR'S SIGNATURE								
0	RESIDENCE & CITIZENSHIP	Fort Collins	STATE OR FOREIGN COUNTRY CO	COUNTRY OF CITIZENSHIP US					
4	POST OFFICE ADDRESS	POST OFFICE ADDRESS GlaxoSmithKline Five Moore Drive, PO Box 13398	Research Triangle Park	STATE & ZIP CODE/COUNTRY NC 27709, US					
2	FULL NAME OF INVENTOR	FAMILY NAME RAJAGOPALAN	FIRST GIVEN NAME Rukmini	SECOND GIVEN NAME/INITIAL					
0	INVENTOR'S SIGNATURE RESIDENCE &	CITY	STATE OR FOREIGN COUNTRY	COUNTRY OF CITIZENSHIP					
}	CITIZENSHIP	Durham	NC	US					
5	POST OFFICE ADDRESS	POST OFFICE ADDRESS GlaxoSmithKline Five Moore Drive. PO Box 13398	Research Triangle Park	NC 27709, US					

COMBINED DECLARATION FOR UTILITY OR DES APPLICATION WITH POWER OF ATTORNEY	ATTORNEY'S DOCKET PU3556USW First Names Inventor. Gordon J. DOW Complete if known:						
(X) Declaration submitted with initial filing or	(f) Declaration submitted with initial filing or						
()Declaration submitted after initial filing (surcharge required 37CFR1.16(e))	Filing Date Group Art Unit:						
As below named inventor. I hereby declare that:							
My residence, post office address and citizenship are as stated below next	to my name.						
I believe I am the original, first and sole inventor (if only one name is lister (if plural names are listed below) of the subject matter which is claimed an entitled:	d below) or an original, f d for which a patent is so	irst and joint inventor ought on the invention					
entitled: FLUTICASONE LOTION HAVING IMPROVED VAS the specification of which (check only one item below): []is attached hereto. OR	FLUTICASONE LOTION HAVING IMPROVED VASOCONSTRICTOR ACTIVITY the specification of which (check only one item below):						
[]is attached hereto. OR							
[x] was filed on 20 October 1999 as United States application Serial No	or PC ?	Γ International					
	DD/YYYY)	(if					
Application Number PCT/GB99/03472 filed and was amended on (MM/lapplicable) I hereby state that I have reviewed and understand the contents of the above as amended by any amendment specifically referred to above.	ve-identified specification	n, including the claims,					
I acknowledge the duty to disclose information which is material to patent	ability as defined in 37 C	FR §1.56.					
I hereby claim foreign priority benefits under 35, U.S.C. §119 (a)-(d) or §365(b) of any foreign applications(s) for patent or inventor's certificate or 365(a) of any PCT international application which designated at least one country other than the United States of America, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate or of any PCT international application having a filing date before that of the application on which priority is claimed:							
PRIOR FOREIGN AND ANY PRIORITY CLAIMS UNDER 35 U.S.C. 119:	Foreign Filing Date	PRIORITY					
Prior Foreign Application Country Number (s)	(MM/DD/YYYY))	CLAIMED					
1. 9823036.0 GB	22 October 1998	X					
3.							
4.							
5.							
I hereby claim the benefit under Title 35, United States Code §119(e) of any Unite Application No. Filing Date (MM/I		cation(s) listed below:					
1.							
2.							
3.							
5.							

Express Mail Label EL395942518US

ATTORNEY'S DOCKET NUMBER PU3556USW

I hereby claim the benefit under 35, U.S.C. §120 of any United States application or §365(c) of any PCT international application designating the United States of America that is listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of 35 U.S.C. §112, I acknowledge the duty to disclose information which is paragraphed by the first paragraph of 35 U.S.C. §112, I acknowledge the duty to disclose information which is paragraphed by the first paragraph of 35 U.S.C. §112, I acknowledge the duty to disclose information which is paragraphed by the first paragraph of 35 U.S.C. §112, I acknowledge the duty to disclose information which is paragraphed by the first paragraph of 35 U.S.C. §112, I acknowledge the duty to disclose information which is the prior application (s) and the national or paragraphed by the first paragraph of 35 U.S.C. §112, I acknowledge the duty to disclose information which is the prior application (s) and the national or paragraphed by the first paragraph of 35 U.S.C. §112, I acknowledge the duty to disclose information which is the prior application (s) and the national or paragraphed by the first paragraphed by the first paragraph of 35 U.S.C. §112, I acknowledge the duty to disclose information which is the prior application (s) and the national or paragraphed by the first
	PCT international fili	ng date of this application:						
PRIOR	U.S. PARENT A	PPLICATION or PO	CT PARENT AP	PLICATION	ON			
						STATUS (Check one)		
U.S. P	arent Application or l Number	PCT Parent	Parent Filing Da (MM/DD/YYY)		PATENTED	PENDING	ABANDONED	
POWER (OF ATTORNEY: A	s a named inventor, I hereb	y appoint the follows	ing attorney(s)	and/or agent(s) to pros	ecute this application a	nd transact all business in	
the U.S. Pa	atent and Trademark	Office connected therewith	. (List name and regi	stration numb	er)		1	
						Dannia I Dannanhr	ock Reg. No. 28,209	
	d J. Levy	Reg. No. 27,655	James P. I	Riek C. Bennett	Reg. No. 39,009 Reg. No. 37,092	John L. Lemanowicz	Reg. No. 37,380	
	les E. Dadswell	Reg. No 35,851 Reg. No. 39,337	Frank P.C		Reg. No. 31,164	John E. Zomano		
Kare	en L. Prus ert H. Brink	reg. No. 36,094		er P. Rogers	Reg. No. 36,334		\	
	abeth Selby	Reg. No. 38,298	Lorie Ani		Reg. No. 38,181			
LI Eliza	abean belog							
Send Co	orrespondence to:		HANNI			Direct Telephone Ca	alls to:	
	orrespondence to: David J. Levy, Pate	ent Counsel				Christon	her P. Rogers	
2 E E	Global Intellectual	Property Department	1102112				483-1240	
	Glaxo Wellcome In	ic.		23347		717	403 12 10	
74.5	Five Moore Drive,		PATEN	IT TRADEMARK	OFFICE	İ	ļ	
8	Research Triangle	Park, NC 27709						
	_					. 11	1	
#= ##=	I hereby declare	that all statements ma	ade herein of my	own knowl	edge are true and tl	nat all statements m	ade on information	
ń	and belief are be	lieved to be true; and	further that these	statements	were made with the	ie knowledge that v	vilitul taise	
###	statements and t	he like so made are p	unishable by fine	or imprisor	ment, or both, und	ler 18 U.S.C. 1001,	and that such	
Total	Statements and t	ements may jeopardiz	e the validity of t	the annlicat	ion or any patent is	suing thereon.		
	William Taise Stat	ements may jeopardiz	c the validity of	ine appirent				
I main	FULL NAME	FAMILY NAME		RST GIVEN NA	ME	SECOND GIVEN NAME	E/INITIAL	
2	OF INVENTOR	DOW	G	Gordon		J.		
	INVENTOR'S		· · · · · · · · · · · · · · · · · · ·			j		
	SIGNATURE					COUNTRY OF CITIZE	NCHID	
0	RESIDENCE &	CITY		STATE OR FOREIGN COUNTRY CA		COUNTRY OF CITIZENSHIP US STATE & ZIP CODE/COUNTRY		
1	CITIZENSHIP	Petaluma						
	POST OFF-CF	POST OFFICE ADDRESS	I Calamaa	CITY		C' 94954, US		
1	ADDRESS	Dow Pharmaceuti		Petaluma		(, 1, 7, 7, 5, 1, 0, 5		
]		1330A Redwoodw	ay			SECOND GIVEN NAM	EGNITIAI	
	FULL NAME	FAMILY NAME		FIRST GIVEN	NAME	Arthur	E/HVIIIAL	
2	OF INVENTOR	JOHNSON		Keith		Attnur		
	INVENTOR'S							
	SIGNATURE			TATE OR FORE	ICN COUNTRY	COUNTRY OF CITIZE	ENSHIP	
0	RESIDENCE &	Durham		NC	IGH COUNTAI	US		
1	CITIZENSHIP	The second of the second		T CITY		STATE & ZIP CODE/C	COUNTRY	
	POST OFFICE	GlaxoSmithKline		Research	rriangle Park	NC 27709, US		
2	ADDRESS	Five Moore Drive, PO	Box 13398		-	'		
	FULL NAME	FAMILY NAME	F	FIRST GIVEN NA	ME	SECOND GIVEN NAM	IE/INITIAL	
2	OF INVENTOR	KELLY		Frances		Furr		
	INVENTOR'S							
	SIGNATURE	1						
0	RESIDENCE &	CITY			E OR FOREIGN COUNTRY COUNTRY OF CITIZENSHIP		ENSHIP	
	CITIZENSHIP	Durham		NC		US		
	POST OFFICE	POST OFFICE ADDRESS		CITY		STATE & ZIP CODE/		
3	ADDRESS	GlaxoSmithKline		Research T	riangle Park	NC 27709, US	ı	
1		Five Moore Drive, PO	Box 13398					

APPI	CICATION WITH	ATION FOR UTILITY OF POWER OF ATTORNEY filing or large (surcharge required 37CFR1.16(e))	R DESIGN PATENT	ATTORNEY'S DOCKET PU3556USW First Names Inventor: Gordon J. DOW Complete if known: App No.: Filing Date Group Art Unit:
	As below named	inventor. I hereby declare that:		
	My residence, post office a	address and citizenship are as stated bel	ow next to my name.	
	I believe I am the original, (if plural names are listed entitled:	first and sole inventor (if only one nan below) of the subject matter which is cl	ne is listed below) or an original, aimed and for which a patent is s	first and joint inventor ought on the invention
	FLUTICA the specification of which	SONE LOTION HAVING IMPROV. (check only one item below):	ED VASOCONSTRICTOR AC	TIVITY
	[]is attached hereto. OR [x] was filed on 20 Octo	ber 1999 as United States application	Serial No or PC	T International
	applicable)	F/GB99/03472 filed and was amended		
	as amended by any amend	reviewed and understand the contents of the difference of the diff		
TOTAL TOTAL		disclose information which is material		
E man is	or inventor's certificate or	ority benefits under 35, U.S.C. §119 (a : 365(a) of any PCT international applic, listed below and have also identified becate or of any PCT international applic	cation which designated at least or below, by checking the box, any f	oreign application for
		RIORITY CLAIMS UNDER 35 U.S.	C. 119:	PRIORITY
Pri	ior Foreign Application Number (s)	Country	Foreign Filing Date (MM/DD/YYYY))	CLAIMED
1. 98	23036.0	GB	22 October 1998	X
3.				
4.				
5.			77 :: 10:	1:ti-n(a) listed below:
I here	by claim the benefit under T Application No.	Title 35, United States Code §119(e) of	any United States provisional apparte (MM/DD/YYYY)	neation(s) fisted below:
1.	Application No.	Timig De	iic (MINIDD) 1111)	
2.				
3.				
4.				

ATTORNEY'S DOCKET NUMBER

PU3556USW

I hereby claim the benefit under 35, U.S.C. §120 of any United States application or §365(c) of any PCT international application designating the United States of America that is listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of 35 U.S.C. §112, I acknowledge the duty to disclose information which is material to patentability as defined in 37 C.F.R. §1.56 which became available between the filing date of the prior application(s) and the national or PCT international filing date of this application:

JOK	U.S. PARENT A					STATUS (Check	one)
U.S. Parent Application or PCT Parent Number		PCT Parent	Parent Filing Date (MM/DD/YYYY)		PATENTED	PENDING	ABANDONED
WER (OF ATTORNEY: A	s a named inventor, I her	eby appoint the foll	lowing attorney(s) and/or agent(s) to pr	osecute this application	and transact all busines
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